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A failure modes and effects analysis quality management framework for image-guided small animal irradiators: A change in paradigm for radiation biology

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Purpose: Image-guided small animal irradiators (IGSAI) are increasingly being adopted in radiation biology research. These animal irradiators, designed to deliver radiation with submillimeter accuracy, exhibit complexity similar to that of clinical radiation delivery systems, including image guidance, robotic stage motion, and treatment planning systems. However, physics expertise and resources are scarcer in radiation biology, which makes implementation of conventional prescriptive QA infeasible. In this study, we apply the failure modes and effect analysis (FMEA) popularized by the AAPM task group 100 (TG-100) report to IGSAI and radiation biological research.

Methods: Radiation biological research requires a change in paradigm where small errors to large populations of animals are more severe than grievous errors that only affect individuals. To this end, we created a new adverse effects severity table adapted to radiation biology research based on the original AAPM TG-100 severity table. We also produced a process tree which outlines the main components of radiation biology studies performed on an IGSAI, adapted from the original clinical IMRT process tree from TG-100.

Using this process tree, we created and distributed a preliminary survey to eight expert IGSAI operators in four institutions. Operators rated proposed failure modes for occurrence, severity, and lack of detectability, and were invited to share their own experienced failure modes. Risk probability numbers (RPN) were calculated and used to identify the failure modes which most urgently require intervention.

Results: Surveyed operators indicated a number of high (RPN >125) failure modes specific to small animal irradiators. Errors due to equipment breakdown, such as loss of anesthesia or thermal control, received relatively low RPN (12–48) while errors related to the delivery of radiation dose received relatively high RPN (72–360). Errors identified could either be improved by manufacturer intervention (e.g., electronic interlocks for filter/collimator) or physics oversight (errors related to tube calibration or treatment planning system commissioning). Operators identified a number of failure modes including collision between the collimator and the stage, misalignment between imaging and treatment isocenter, inaccurate robotic stage homing/translation, and incorrect SSD applied to hand calculations. These were all relatively highly rated (90–192), indicating a possible bias in operators towards reporting high RPN failure modes.

Conclusions: The first FMEA specific to radiation biology research was applied to image-guided small animal irradiators following the TG-100 methodology. A new adverse effects severity table and a process tree recognizing the need for a new paradigm were produced, which will be of great use to future investigators wishing to pursue FMEA in radiation biology research. Future work will focus

on expanding scope of user surveys to users of all commercial IGSAI and collaborating with manufacturers to increase the breadth of surveyed expert operators. © 2020 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.14049]

Key words: FMEA, image-guided small animal irradiators, radiation biology

1. INTRODUCTION

Considerable technological advances have resulted in the recent development of kilovoltage (kV) image-guided conformal small animal irradiation (IGCSAI) systems. As opposed to conventional cabinet-style kV x-ray irradiators, these new devices offer cone-beam CT (CBCT) and often bioluminescence image (BLI) guidance, treatment planning software (TPS) to calculate dose to tissues, determine beam angles, exposure times, dose distributions, dose volume histograms (DVH), image registration, and contouring and segmentation of targets or organs-at-risk (OARs). This often includes robotically driven couch systems to position the target with submillimeter accuracy. Two commercially available IGCSAI systems currently exist: the Xstrahl Small Animal Radiation Research Platform (SARRP)^{1,2} (Xstrahl, Atlanta, GA, USA), and the Precision X-ray (PXi) Small Animal RadioTherapy (SmART) system^{3,4} (Precision X-ray, North Branford, CT, USA). However, despite the rapid influx of new technology, comprehensive quality assurance (QA) protocols similar to the AAPM TG-142⁵ for linear accelerator are still virtually nonexistent, and radiation biology study protocols present wide variations from site to site.^{6–10}

Many attempts have been made to produce rigorous systematic and prescriptive QA^{11–17} methodologies similar to those employed in the clinic for patient radiation therapy (RT) such as the AAPM Task Group 40¹⁸ and 142.⁵ These approaches typically focus on comprehensive dosimetry and geometrical tests performed by physics specialists with knowledge and access to specialized equipment such as special dosimetric phantoms,^{16,19} GAFChromic EBT film,^{15,20} alanine detectors,²¹ and ionization chamber measurements. Under these circumstances, expecting IGSAI operators mainly trained in biology or animal experiments^{7,8} to perform prescriptive QA regimen with little to no physics expertise and without access to specialized equipment is unrealistic. Furthermore, prescriptive and systematic QA procedures measure all aspects of an irradiator's performance, but with little to no emphasis placed on which aspects are more likely to lead to radiation delivery errors.

In this study, we apply the American Association of Physicists in Medicine (AAPM) Task Group 100 (TG-100) Failure Modes and Effects Analysis (FMEA) methodology²² to apply modern risk-based analysis techniques to IGCSAI, as it has been done for a number of other medical physics applications.^{22–35} In the process, we propose a new process map specific to IGCSAI that changes the paradigm from individual errors in radiation delivery, to groups that are highlighted in a proposed new severity table. We also perform a preliminary FMEA survey based on expert opinion from SARRP operators.

2. MATERIALS AND METHODS

The FMEA for IGCSAI was performed following the FMEA methodology outlined in the AAPM's TG-100 by a team of eight operators from four radiation biology laboratories. Contributions were provided by physicists, researchers, and laboratory technicians performing radiation biology experiments.

2.A. Failure modes and effects analysis: a quick overview

As FMEA methodology has been extensively described in the original AAPM TG-100 report²² along with countless other clinical applications too numerous to list, we will limit ourselves to a brief overview.

Failure modes and effects analysis methodology highlights situations in which a process (i.e., a radiation study) might fail its objectives. This failure can be any error or defect, and can have multiple root causes. Each root cause is associated with a failure mode; a specific pathway in which the failure occurs. In turn, each of these vary in Occurrence (O), Severity (S), and lack of Detectability (D). The occurrence refers to how likely the failure mode is to occur, the severity refers to how serious the adverse effects (AE) are if the failure mode is not detected, and the lack of detectability refers to the likelihood that the failure mode will be not be detected before the adverse effect occurs. Each of these parameters are assigned a value ranging from 1 to 10, with 1 signifying lowest risk and 10 highest risk, and a *Risk Priority Number* (RPN) is then the product of these three values

$$RPN = O \times S \times D \quad (1)$$

where the RPN can range from 1 (lowest risk) to 1000 (highest risk), and interventions such as quality assurance tests or increased documentation can be targeted at the highest scoring values, thereby encouraging efficient use of resources.

These values for O, S, and D are ideally determined using quantitative and statistical analyses based on measured occurrences and detectability. However, as per TG-100, expert testimony and predictions can substitute for quantitative values in preliminary analyses where quantitative values do not yet exist. These quantitative values are then acquired over time once a proper framework has been established.

2.B. Traditional cabinet irradiators

According to a recent survey, the vast majority (>75%) of radiation biology experiments are performed using cabinet style irradiators using either Co-60, Cs-137, or kV x rays.¹⁰

Very briefly and generally, cabinet style irradiators tend to operate with a fixed radiation source, be it Cs-137, Co-60, or kV x-ray tubes. Their collimation and source-to-surface distances (SSD) can either be fixed or variable. Digital or analog field size or SSD indicators are usually nonexistent. While Cs-137 and Co-60 have fixed beam qualities and dose rates which depend entirely on the source activity, kV irradiators can vary their beam quality through varying peak kilovoltage (kVp) and filtration, and their beam intensity through kVp, filtration, and tube current (mA).

There are few authoritative recommendations on how to operate and design radiobiological studies in cabinet irradiators except for the *Protocol for X-ray Dosimetry* published by the European Late Effects Project Group (EULEP) in 1985 and updated in 2001.^{36,37} In general, a distinction is made between total body irradiation techniques, which are conceptually simple, and partial body irradiations (PBI) where shielding must manually be placed to collimate the x-ray field and/or shield a specific area of the body. PBI is useful for bone-marrow sparing techniques where investigators wish to avoid the hematopoietic syndrome to study other high-dose biological endpoints. While cabinet irradiators are used to deliver single field irradiations,¹⁰ a parallel-opposed field configuration is suggested when the thickness of the subject exceeds 5 mm³⁷ although this typically entails manually repositioning the animal between beams, which increases the risk of failing to reproduce the position of the animal or the shielding with in the case of PBI.

The vast majority of traditional cabinet irradiators possess no integrated imaging system, and the user is limited to the use of visual inspection, light fields, or portal radiographic films to ensure accurate positioning. Certainly there is no CBCT, robotic stage, treatment planning system, bioluminescence-integrated imaging, etc. However, as these irradiators contain relatively few moving parts (field size, SSD, beam quality for kV irradiators, and manual shielding/collimation), there are much fewer potential failure modes in comparison to more modern image-guided irradiators. For this reason, traditional cabinet irradiators are typically thought to be more robust than IGCSAI to failure modes, although no quantitative analysis has been performed.

2.C. Modern Image-guided conformal small animal irradiators

Modern image-guided radiation research platforms include CBCT used for both treatment simulation, localization, and delivery, and take advantage of a robotic stage capable of submillimeter accuracy in motion.^{1,38–40} Recently published guidelines by ESTRO-ACROP provide detailed description of the current technological status of these units, as well as recommendations as to their operation, developing workflow, and which aspects should be commissioned before use.¹⁷

Both commercially available systems are similar but have some subtle differences. The Xstrahl SARRP acquires CBCT images using a stationary x-ray tube and detector while

rotating the couch 360°, whereas the PXi XRAD-SmART acquires CBCT images using a more traditional geometry where the source and detector rotate 360° around the stationary couch. Both systems are capable of portal imaging — the XRAD-SmART using its CT detector aligned with the x-ray tube both for CBCT and portal imaging, and the SARRP using a separate dedicated camera mounted on the gantry, or using the CT detector panel if imaging at 90°. This dedicated camera on the SARRP is only 5 cm² × 5 cm², so there are some limitations to the achievable field of view. Specifications of each irradiator are presented in Table I.

Both units feature isocentric radiation delivery with a gantry capable of full 360° rotations. Both have robotic stages that govern the position of the animal during treatment delivery that can be used to align the animal to conform with the location of the isocenter in the treatment plan. The SARRP couch and gantry are both capable of rotating 360° which allows noncoplanar beam delivery, whereas the XRAD-SmART couch does not rotate — the manufacturer instead offers a “mouse roulette” placed on the stage that can rotate the animals between fields.

Both systems are equipped with a TPS. At the time of writing, the SARRP uses a kernel-based superposition–convolution algorithm similar to those used clinically for MV x rays, although a Monte Carlo alternative has very recently been released.^{15,20} In general, kernel-based superposition

TABLE I. Specifications (nominal) for both commercial IGCSAI systems.

Specification		Xstrahl SARRP	PXi SmART
Beam quality (nominal)	Acc. potential	220 kVp	225 kVp
	Added filtration	0.15 mm Cu	0.30 mm Cu
	Half-value layer	0.65 mm Cu	0.90 mm Cu
	Dose rate ^a	3.6 Gy/min	4.0 Gy/min
Focal spot size	Therapy	3.0 mm	3.0 mm
	Imaging	0.4 mm	0.4 mm
Treatment planning system		Superposition–convolution/Monte Carlo	Monte Carlo
Geometry	Source-to-isocenter	35 cm	30.7 cm
	Source-to-detector	50 cm	60 cm
	Max. Field size ^b	1 cm ² × 1 cm ² / 4 cm ² × 8 cm ² / 10 cm ² × 12 cm ²	3 cm ² × 4 cm ² / 10 cm ² × 10 cm ² / 10 cm ² × 10 cm ²
Imaging	Detector size	20 × 20 cm ²	20 × 20 cm ²
	Voxel size	230–330 μm	200 μm
	Energy	40–80 kVp	40–100 kVp
	Filtration	1 mm Al	2 mm Al

^aAt isocenter.

^bLeft: maximum fixed collimator size; right: motorized variable collimator (MVC) system; bottom: open field size.

algorithms struggle to model the complex interplay of near-isotropic scattering and photoelectric interactions at kV energies,^{41–43} although this is mitigated by the small aperture sizes used in IGCSAI. In contrast, the XRAD-SmART uses a full Monte Carlo model which more accurately models the physical interactions at kV energies.³

Both systems can be upgraded to be capable of online bioluminescence imaging to localize the tumor prior to treatment delivery. Since the CBCT has limited soft tissue resolution, these systems can be used to aid in orthotopic tumor treatment delivery.^{44,45}

2.D. Preliminary process tree

Figure 1 shows our proposed preliminary process tree specific to IGCSAI radiobiological experiments, containing 8 major steps and 38 substeps. We used the AAPM’s TG-100 process map specific to IMRT²² as a starting point and adapted it for IGCSAI by removing all steps specific to human RT while incorporating new steps specific to radiation biology studies. While commissioning and validation are important components of any research program, only steps intrinsic to routine operation of the device are included in this process tree.

Radiation biology studies are similar in certain aspects, but distinct from clinical RT in others. For

instance, diagnostic and clinical workup tasks which are used to diagnose disease and prescribe the treatment in clinical RT are replaced by a study design phase in radiation biology where a specific tumor model is chosen to be deliberately implanted in the subject. Clinical RT relies on record-and-verify systems to ensure privacy, accuracy, and continuation of patient medical records as they receive treatment; these steps are not necessary in radiation biology where a single animal ID and study number designation amply serve to identify biological subjects.

In contrast to clinical RT where simulation, planning, and delivery are separated by days or weeks, radiation biology experiments are typically planned and delivered on the same day in a single fraction using a unique CBCT to identify, plan, localize, and treat the target. Therefore, while there is no formal requirement for CT simulation, secondary imaging (e.g., micro-CT, MRI or bioluminescence imaging, typically acquired outside the irradiator in a specialized small animal imaging core) can be fused to better identify the target (under step 3, marked as optional in Fig. 1). Anatomy contouring (step 4 in Fig. 1) is mandatory in clinical RT but optional in IGCSAI, with many sites being treated without formal delineation of either the target or the OARs due to operational constraints such as time, anesthesia, thermal control, or lack of sufficient contrast in the planning CBCT to identify them.

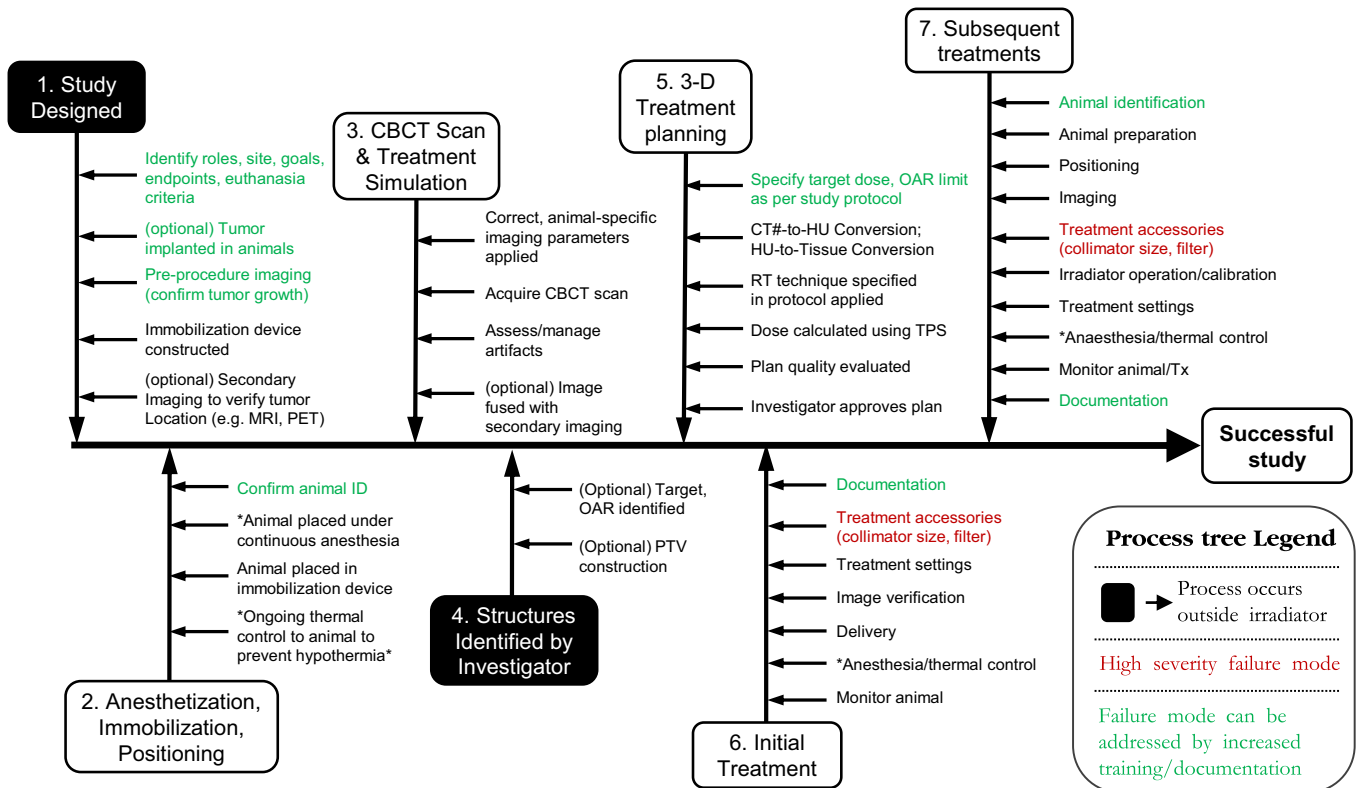


FIG. 1. Tentative process tree specific to image-guided small animal irradiation studies. Grayed out boxes indicate steps of the process which are not strictly performed at the irradiator (step 4 could be performed a priori on fused images). Asterisks indicate steps which are new and specific to small animal irradiations. Red and green items (online version only) represent steps we identified as being most and least at risk, based on the computed RPN, respectively. [Color figure can be viewed at wileyonlinelibrary.com]

2.E. Severity table

2.E.1. Original severity table from AAPM Task Group-100

The original AAPM TG-100 report contains a table of severity factors (1–10, with 10 being most severe) for relevant adverse effects in clinical RT following a relatively simple framework: high risks to the individual are scored more aggressively than moderate risks to populations. The majority of severity terms fall into two categories. The first, termed *wrong X* (where X is either the dose distribution, absolute dose, location for dose, or volume), indicates small errors applied to a group of patients, and was scored moderately high (S = 5–8). The second, termed *very wrong X*, instead indicated large errors to a single individual, and was scored very high (S = 9–10). These reflect the central philosophy in medicine in which a manageable toxicity or reduced chance of tumor control in a group of patients is not as severe as grievous harm or a loss of tumor control in a single individual.

Four additional severity terms vary in severity score — a “suboptimal plan” (S = 4) describes a plan capable of marginal improvement without risk of control loss or severe side effects. Inconvenience to the patient (S = 2–3) is scored higher than inconvenience to the staff or increased cost (S = 1–2) as it is the duty of the hospital staff to accommodate patients. Finally, “nonradiation-related physical injuries” (e.g., gantry collision with patient resulting in injury, fracture, or death) had a wide but high severity score range (S = 5–10) to reflect the wide range of possible outcomes.

These adverse effect categories and severity values show the core philosophy of the AAPM TG-100 methodology applied to clinical RT. In short, the risks to the individual outweigh the risks to the population; an error leading to a statistically detectable change in tumor control or OAR toxicity in a population is still severe, but less so than a catastrophic injury to an individual patient. The RT clinic is also assumed to be well resourced, such that it can afford to place patient convenience above operational concerns for its own staff.

2.E.2. Proposed new severity table for IGCSAI

Applying the AAPM TG-100 framework to radiation biology requires an entirely different philosophy — a change in paradigm. In the clinical environment, the worst possible outcome is the death or severe toxicity of a patient due to a grievous error during radiation therapy treatment. However, research animals are destined from the onset to be sacrificed according to previously established euthanasia protocols following clear criteria. As such, the death of an animal, instead of being a catastrophic event, is often the measured endpoint. Therefore, we inverted the severity ratings for the risk categories *very wrong X* (large error to individual) with those of *wrong X* (small error to populations). A comparison of the original S values and our proposals is shown in Table II. While the original TG-100 report did not posit the magnitude

TABLE II. Comparison between severity terminology in AAPM TG-100 (left) and specific to image-guided animal irradiators (right). Terms bolded in red have increased while terms italicized in blue have decreased.

TG-100 severity terms	TG-100 S values	Small-animal irradiator severity terms	Proposed S values
Wrong dose distribution	5–8	Small error in dose distribution for population of animals	9–10
Very wrong dose distribution	9–10	Large error in dose distribution for single animal	<i>5–8</i>
Wrong absolute dose	5–8	Small error in absolute dose for population of animals	9–10
Very wrong absolute dose	9–10	Large error in absolute dose for single animal	<i>5–8</i>
Wrong location for dose	5–8	Small geometrical error in dose delivery for population of animals	9–10
Very wrong location for dose	9–10	Large geometrical error in dose delivery for single animal	<i>5–8</i>
Wrong volume	5–8	Small error in volume delineation for population of animals	9–10
Very wrong volume	9–10	Large error in volume delineation for single animal	<i>5–8</i>
Suboptimal plan	4	Small deviation in plan from study protocol	4
Nonradiation-related physical injury	5–10	Unanticipated euthanasia/death from error during irradiation	<i>5–8</i>
Inconvenience — patient	2–3	Preventable stress, pain, or distress to animal	<i>1–2</i>
Inconvenience — staff or increased cost	1–2	Inconvenience — staff or increased cost	3–4

of a “wrong” compared to a “very wrong” dose delivery error, it did suggest 5–10%/3–5 mm in the former and 10–20%/>5 mm for the latter. Absent from this table (and the original TG-100 Severity table) are entries corresponding to small errors to individuals or large errors to populations. In the case of the former, they are encapsulated by the “sub-optimal plan”/“small deviation from study protocol,” whereas, the latter represent a larger magnitude of the “small error for population of animals.” As Severity is capped at 10, already within the range of severity for this adverse effect, a separate entry is not required.

It is very difficult to suggest exact values in the context of the newly proposed severity table. A 5–10% error in radiation biology would certainly be sufficient to cause a statistically detectable variation in study outcome due to the very high gradients in some radiation dose effect relationships,⁴⁶ but perhaps not others. Likewise, the consequence of a radiation delivery to the wrong area will depend much more acutely on the specifics of the endpoint being studied than in the clinic, where tumor control (even if transient for symptom management) is typically the intent of most radiotherapy courses. In reality, however, these values remain subjective, and more attention should be placed on the big picture of groups vs individuals, rather than on specific thresholds.

TABLE III. Original survey circulated to operators in preliminary IGCSAI FMEA study.

Process step	Failure mode	Cause	Adverse effect	O	S	D	RPN
Immobilization	Loss of anesthesia	Operator mistake Collision between unit and anesthesia delivery	Inconvenience to operator (need to image/plan again) Preventable stress/pain/distress to animal				
	Loss of thermal control	Operator mistake Equipment failure	Inconvenience to operator Unanticipated death/euthanasia				
Treatment planning	Incorrect dose assigned to target	Operator mistake Error in documentation	Small or large error in dose to single animal Small or large error in dose distribution to single animal				
Treatment delivery	Tube output incorrectly reported	Error in commissioning Incorrect output factor applied	Small error in absolute dose to population of animal Large error in absolute dose to population of animal				
	Incorrect beam accessories applied: e.g., collimator/filter	Lack of interlock	Large error in absolute dose to single animal				

Some terms changed meaning entirely when moving from clinical RT to radiation biology. We replaced “suboptimal plan” with “small deviation in plan from study protocol,” which conveys the same meaning applied to a radiation biology context. The “nonradiation related physical injury” adverse effect was changed to “unanticipated euthanasia or death from error during irradiation,” which carries a lower severity rating in radiation biology compared to clinical RT. Nevertheless, repeated unanticipated euthanasia can result in the ethics of the study being put into question and potentially threaten the continuation of the study, so the severity rating was maintained to a relatively high range of 5–8. Finally, the rating for inconvenience to the patient vs. staff are swapped in radiation biology, as inconvenience (here interpreted as preventable stress to the animal) is a relatively minor concern, but investigators have fewer resources to accommodate increased costs and disruptions in schedule.

2.F. Preliminary survey

We created a preliminary survey (see Table III) and distributed it to a group of four sites that perform radiation biology studies using the Xstrahl SARRP, with a total of eight operators contributing to the survey. However, the same methodology could also be used for other IGCSAI units, including the PXi XRAD-SmART or any noncommercial platform.

The original survey was kept intentionally small to encourage compliance, and therefore only featured five proposed failure modes that we deemed most indicative of the common errors in IGCSAI. Operators were asked to score each individual failure mode, despite multiple possible causes, in terms of single O and D according to Table II from the AAPM TG-100, and S in terms of the new severity table we proposed, respectively.

In addition to the proposed failure modes, operators were asked to contribute any additional failure modes they had personally encountered or failure modes that they conceived

were possible. Finally, operators were invited to comment on each proposed or volunteered failure modes.

3. RESULTS

3.A. Preliminary survey

Operators ranked our proposed five failure modes in terms of occurrence, severity, and lack of detectability. For each individual response, the RPN was calculated, and whole ranges are shown in Table IV. According to this original survey, the highest risk failure modes were both related to treatment delivery: namely, incorrect dose delivered to entire groups of animals due to errors in tube output or errors in irradiating individual animals due to incorrectly applying beam collimators.

Incidentally, more common failure modes such as loss of anesthesia or thermal control, received a very low RPN. The only failure mode proposed for TPS received a consistently moderate score according to all operators.

3.B. Volunteered failure modes from surveyed operators

Table V lists failure modes volunteered by Xstrahl SARRP operators who participated in our preliminary FMEA survey. In total, four failure modes were identified — two in treatment planning and two in treatment delivery. Interestingly, no failure modes associated with immobilization/treatment preparation were suggested. In each case, operators described these errors as they had occurred in their own radiation biology laboratory.

4. DISCUSSION

Eight operators from four institutions filled out a preliminary FMEA survey of five proposed failure modes and proposed a further four failure modes. The RPN of the FMEA

TABLE IV. Results of survey distributed to operators and ranges of O, S, D, and RPN.

Process step	Failure mode	Cause	Adverse effect	O	S	D	RPN
Immobilization	Loss of anesthesia	Operator mistake Collision between unit and anesthesia delivery	Inconvenience to operator (need to image/plan again) Preventable stress/pain/distress to animal	3-4	3-4	1-3	12-27 (18)
	Loss of thermal control	Operator mistake Equipment failure	Inconvenience to operator Unanticipated death/euthanasia	2-4	3-5	2-4	18-60 (24)
Treatment planning	Incorrect dose assigned to target	Operator mistake Error in documentation	Small or large error in dose to single animal Small or large error in dose distribution to single animal	2-5	6-8	5-8	72-320 (126)
Treatment delivery	Tube output incorrectly reported	Error in commissioning Incorrect output factor applied	Small error in absolute dose to population of animals Large error in absolute dose to population of animals	2-5	8-10	5-10	200-270 (224)
	Incorrect beam accessories applied: e.g., collimator/filter	Lack of interlock	Large error in absolute dose to single animal	2-5	6-10	6-10	160-360 (240)

TABLE V. Volunteered failure modes by SARRP operators.

Process step	Failure mode	Cause	Adverse effect	O	S	D	RPN	
Imaging/Treatment planning	Misalignment between radiation and imaging isocenters	Misalignment in tube position from push and pull of inserting/removing collimator Prior collision	Incorrect dose calculation Potential tumor underdosing Potential OAR overdosing Reduced image quality		3	8	8	192
Treatment planning	Incorrect SSD entered	Operator mistake Error in documentation	Small or large error in dose to single animal Small or large error in dose distribution to single animal		3	5	6	90
Treatment Delivery	Incorrect couch positioning for therapy	Incorrect homing Incorrect motor stepping	Small or large error in dose for single animal Small or large error in dose distribution for single animal		3	5	6	90
	Collision between gantry and stage	Lack of interlock	Large error in absolute dose to single animal		3	8	8	192

survey and proposed failure modes vary from 27 to 360. In general, all surveyed operators agreed on which failure modes carried the highest risk — loss of anesthesia and thermal control were seen as relatively trivial, whereas errors in dosimetry and commissioning were consistently seen as high priority risks as they affect every single dose delivery.

The reason is simple — compared to more common clinical applications such as MV x rays, MV electrons, and protons, kV x rays are relatively underserved in medical physics. In kV x-ray dosimetry, the majority of detectors exhibit increased energy dependence compared to the MV and proton energies commonly used in the clinic. The AAPM TG-61⁴⁷ and the IAEA TRS-398⁴⁸ provide general calibration protocols for clinical superficial and orthovoltage kV x-ray units. These units are similar enough in terms of beam quality to the small animal irradiators to be applicable, but assume a large (>4 cm) field with infinite backscatter, which is not the case in most radiation biology experiments.^{10,49} This is particularly true for IGCSAI, where the majority of fields are

≤2 cm in size. For this reason, there exist large differences between the dose rate measured under calibration conditions and the dose rate delivered under experimental conditions.⁴⁹ In fact, EULEP is the only widely known protocol for conducting radiation biology experiments, and recommends measuring dose under experimental conditions using animal-specific phantoms,³⁷ but it dates back to 2001 when IGCSAI systems were not yet in use. Thus, it is particularly important to ensure the accuracy of the commissioning of IGCSAI systems.

Commissioning has widely been performed using GAF-Chromic film,^{3,4,15} as it is currently the only dosimeter with small enough resolution to measure the dose for ≤1 cm field sizes, with an acceptable energy dependence. These difficulties explain why dose characterization was consistently among the largest perceived RPN failure mode in IGCSAI. Indeed, in the past, repeated multi-institution dosimetric surveys have shown how challenging it is to produce accurate and homogeneous dose deliveries consistently across

multiple sites.^{36,37,50,51} Since these audits were performed using the simpler cabinet-style irradiators, one could reasonably expect a wider set of responses still in IGCSAI that may utilize much more complex technology.⁵² In principle, the difference between calibration and treatment delivery is meant to be modeled by the TPS. However, this system is currently commissioned almost exclusively by the manufacturer as a “black box.” In practice, the Xstrahl SARRP Muriplan (version 3) has been shown to have dosimetric deficiencies of up to 20% near a phantom surface.^{14,53}

Finally, the manual use of treatment accessories without electronic interlocks to verify the correct filter and cone sizes were seen as the largest risk of failure (128–360). Given that electronic interlocks are common in other radiation equipment, it is curious that these have not yet been introduced in more recent versions of IGSAI. Indeed, one of the manufacturers (Xstrahl), produces superficial/orthovoltage x-ray therapy devices for clinical use in patients which comprise energy-specific interlocks for the appropriate filter, as well as cone-specific interlocks. Monitor ionization chamber which measure throughput of radiation are another feature common in clinical RT which has not been replicated in IGSAI, although they may be less useful in continuous sources of radiation than for pulsed linacs.

In addition to the initial survey, respondents provided four additional failure modes, three of which focused on errors that arise during the preparation and delivery of radiation (wrong SSD, misaligned tube, collision between gantry and stage) and only one was a systematic mis-calibration of an important parameter such as the couch rotation. Each of the user-proposed failure mode was rated relatively highly (90–192), which is unsurprising since operators are presumably more likely to propose failure modes that they deem important based on prior experience.

In spite of the new severity table, it seems that the majority of operators rated large, individual errors the same as errors which applied to large numbers of animals. This may indicate a bias in operators who prefer to avoid large errors in single animals, even if they have overall a lesser impact on the success of a study, vs a more moderate error that impacts an entire study's conclusions but is less disastrous in scope to any individual animal.

From this preliminary analysis, it appears the main areas where QA can be improved is in ensuring that the correct dose is applied, including adding the presence of beam accessories such as filter and cone size interlocks (RPN 160–360). Furthermore, there is a concern that the dose rate is not correctly characterized (RPN 200–270). This could be addressed via independent third-party dose auditing such as that performed in clinical trials by the Imaging and Radiation Oncology Core (IROC), or in radiobiology cabinet irradiators as performed by Pedersen et al.⁵⁰ or Seed et al.⁵¹ Some of the failure modes submitted by the users did relate to calibration errors that could be caught by conventional prospective QA.¹¹ One less onerous method to avoid resource-intensive prospective QA would be to automate simple mechanical tests using IGCSAI portal cameras in a manner analogous to

the Varian Machine Performance Check in Truebeam Accelerators.^{13,14,53}

Target delineation is a crucial step of the process which requires additional imaging, since CBCT typically fails to provide sufficient contrast to identify tumors. This requires MR,⁵⁴ SPECT,⁵⁵ PET,⁵⁶ or BLI⁴⁵ which are subsequently fused to the planning CT or, in the case of the SARRP, integrated BLI.⁴⁴ While not incorporated in this study due to uneven access across sites, these additional imaging modalities would require their own FMEA by operators familiar with them.

Prescriptive QA protocols such as TG-40¹⁸ or TG-142⁵ do not currently exist for IGSAI. Despite authoritative reviews such as the recently published ESTRO-ACROP guidelines¹⁷ or the proposed monthly QA protocol proposed by Brodin et al.,¹¹ no comprehensive guidelines of tests with proposed tolerances and frequencies have yet been proposed to IGSAI. One of the main obstacles in establishing these guidelines is the uneven access of radiation physics expertise, equipment, time, and knowledge amongst radiation biology operators.^{7,8,37,57} According a recent review,¹⁰ less than 16% of radiation biological publications report any form of dosimetric validation, and remote dosimetry surveys show a majority of sites incapable of reproducing a specific dose.^{36,37,50,51} Recently, the AAPM has established the Task Group 319 to develop guidelines for accurate dosimetry in radiobiology experiments,⁵⁸ but their recommendations will focus nearly exclusively on cabinet irradiators still used in the vast majority of radiation biology experiments.¹⁰ Under these conditions, expecting radiation biology operators to adhere to a full-scale prescriptive QA program such as described by Brodin et al.¹¹ may be unrealistic. In this case, a wider, more in-depth FMEA methodology can help focus the efforts of physicists towards those aspects of IGSAI most in need of QA intervention. One of the advantages of FMEA is to highlight possible failure modes for nonphysicists operators of IGCSAI system. Indeed, while errors such as applying the wrong collimator or filter are probably intuitive to the majority of users, users who lack clinical physics exposure may be less familiar with more subtle failure modes such as errors in calibration. In this regard, an FMEA analysis such as the one produced in this study may serve to highlight the potential sources of error in radiation biology experiments performed by IGCSAI systems.

5. CONCLUSIONS

We applied the FMEA methodology first outlined in the AAPM's TG-100 to IGCSAI. We proposed a new process tree and a new severity table specific to preclinical radiation biology studies, and created a preliminary survey outlining five common failure modes specific to image-guided small animal irradiators. The survey was distributed to eight operators from four institutions engaged in image-guided small animal irradiations.

More importantly, this work represents the first attempt to apply the FMEA framework to preclinical radiation biology

studies. The modifications to the AAPM TG-100 framework, in particular the new severity table, will be useful to other physicists who wish to build upon it.

While this survey was specific to the SARRP operators, the same methodology can be used for all IGCSAI, as well as traditional cabinet-style irradiators. In time, failure modes identified by this process as high RPN can be addressed either by either manufacturer-driven improvements, or targeted QA intervention. Furthermore, these results can help highlight failure modes to biologists who may be otherwise unaware of them. Future work will focus on collaborating with manufacturers to expand the survey to more operators, compiling more failure modes, and establishing fault trees for each failure mode.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to disclose.

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